

# The Biological Exposure Indices: A Key Component in Protecting Workers from Toxic Chemicals

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Biological monitoring of exposure to chemicals in the workplace is an important component of exposure assessment and prevention of adverse health effects. It should be employed in conjunction with ambient air monitoring to provide information on the absorbed dose of a chemical agent and the effect of all routes of exposure. Judgments regarding the acceptable level of a chemical or its metabolite in biological samples are facilitated by comparison to a reference value. The American Conference of Governmental Industrial Hygienists has established a series of recommended reference values called the Biological Exposure Indices (BEI). The history and characteristics of the BEI are reviewed, and their suitability for use by occupational health specialists is examined. A number of challenges and stimuli to the continued development and improvement of these reference values are described, and the impact of recent advances in macromolecular biology is assessed. — *Environ Health Perspect* 105(Suppl 1):105–115 (1997)

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## Introduction

Biological monitoring is generally described as the planned and repeated collection of specimens of tissue or body fluid, for the purpose of estimating the chemical composition of the body's internal environment. The repeated aspect differentiates monitoring from sampling and emphasizes the point that temporal changes in chemical composition are just as important as the estimates at a single time.

Motivations for biological monitoring arise in clinical medicine, forensic toxicology, and occupational hygiene. Medical applications include the repeated sampling of peripheral blood to assess the circulating level of a therapeutic drug given as a means

of treating a diagnosed illness. The biological monitoring data provide the information necessary to adjust the dosing regimen to account for the individual characteristics of the patient and to achieve the desired effect without overexposure. The major application of biological monitoring in forensic toxicology is the periodic sampling of voided urine of workers in certain critical jobs, followed by analysis for evidence of use of incapacitating or illegal drugs or other substances. It should be noted that the collection of a breath sample by a traffic officer who suspects a driver of ethanol intoxication would fit the description of biological sampling but not monitoring. In occupational hygiene, biological monitoring is used as part of an array of techniques for evaluating the worker's risk of health damage due to exposure to chemical agents and it is especially valuable when conducted to indicate exposure to a potentially harmful chemical at a time when preventive measures can be effective in reducing or eliminating the health risk.

Occupational biological monitoring must be viewed as complementary to, and not a replacement for, the more traditional measurement of airborne concentrations of chemical agents (1). It provides additional information that can be of great value in evaluating and controlling risky exposures.

The advantages offered by biological monitoring in the occupational setting have been thoroughly reviewed by others (2–4) and will not be explored here in any detail. This form of exposure monitoring invokes some additional requirements, however, one of which is the existence of reference values against which observed biological concentrations may be compared to form judgments about the acceptability of the workplace conditions.

One substantial collection of reference values for biological monitoring in workplaces is the list of Biological Exposure Indices (BEI) published by the American Conference of Governmental Industrial Hygienists (ACGIH). Organizations such as the ACGIH, together with governmental regulating agencies, perform a key role at the interface between science and policy; ideally, their mission is to use the best available scientific and technical data to set recommended or regulatory limits that will minimize the health risks to workers while maximizing the benefit to society of the economic activity associated with the work.

This review describes the BEI in terms of the philosophy and process under which they are established and the role they play in the practice of occupational hygiene and occupational medicine. The extent to which the BEI meet the expectations of the scientific, regulatory, and practitioner communities will be addressed and their strengths and limitations will be explored. The pace of scientific development offers the opportunity to speculate on directions to be taken in generating or revising the BEI and other reference values for biological monitoring over the next decade.

## Defining Characteristics of the Biological Exposure Indices

The BEI are reference values intended as guidelines for the evaluation of potential health hazards in the practice of industrial hygiene (5). The mission of industrial hygiene is the anticipation, recognition, evaluation, and control of exposure to health hazards in the workplace, with the overall aim of preventing or minimizing adverse health effects of exposure. Thus, when the BEI are used by physicians, nurses, engineers, or industrial hygienists, their principal application should be to support prevention of injurious exposures.

These reference values are the recommendations of a professional society, the

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Abbreviations used: ACGIH, American Conference of Governmental Industrial Hygienists; BAT, biological tolerance values; BEI, Biological Exposure Indices; Nq, nonquantitative; TLV, threshold limit values.

ACGIH, which also establishes reference values for airborne chemical concentrations in the workplace. The latter are called Threshold Limit Values (TLV) and represent conditions under which nearly all workers may be exposed repeatedly over a working lifetime without adverse health effects. It should be noted that the ACGIH is a private organization without regulatory authority and its reference values are offered as recommendations for good practice without guarantee that they are a clear demarcation between safe and unsafe conditions. As presented by the ACGIH, industry compliance with the BEI and the TLV is voluntary. Despite this disclaimer, the TLV and to a lesser extent the BEI have been used by government agencies around the world as the basis for workplace environmental regulations.

The BEI are developed by the BEI Committee of the ACGIH, which consists of volunteer scientists and practicing professionals with expertise in occupational medicine, toxicology, industrial hygiene, analytical chemistry, biostatistics, and epidemiology. The present committee members include specialists from the United States, Japan, Germany, Switzerland, and the United Kingdom employed in academia, government, or private industry (the last category of members does not have voting privileges but otherwise participates fully in the process.) The committee meets twice a year to develop new reference values and to conduct a regular review of existing BEI as new data emerge. Several values have undergone significant revision as a result of such review; examples will be described below.

The BEI are intended for use in biological monitoring where the goal is the determination of the worker's internal, or biologically effective, dose of a chemical. The determinant may be the parent compound itself, metabolite(s), or a characteristic reversible biochemical change induced upon absorption. The index values represent the level of the determinant most likely to be observed in specimens collected from a worker with an internal dose equivalent to that arising solely from inhalation exposure at the TLV concentration (5). Thus, most of the BEI are closely linked to the corresponding TLV and are based on preventing the same health effect addressed by the TLV. This does not imply, however, that airborne concentrations and biological levels must always be correlated in exposed workers, since routes of absorption in addition to inhalation are possible. Where

this occurs, comparison of biological levels to the BEI takes on special importance, since the BEI represents the acceptable internal exposure regardless of the route(s) of entry.

## History of the Development of Biological Exposure Indices

Biological monitoring has been used as one of several complementary tools for assessing worker exposure to chemicals for at least 60 years (6)—more widely in Europe than in the United States (7). The present general concept of biological monitoring reference values used by the ACGIH can be attributed to the work of Elkins (8,9) beginning in 1954. He noted that knowledge of metabolism and excretion of each specific chemical was necessary to interpret results properly and he presented a series of recommended biological exposure limit values for solvents.

### American Conference of Governmental Industrial Hygienists' Threshold Limit Values Committee

The ACGIH recognized the value of the concept of biological monitoring in the early 1970s, and in 1973 first included a discussion of biological limit values in its annual listing of TLV (10), although no values were adopted at that time. During the subsequent decade there was considerable debate over the ACGIH role in biological monitoring and medical surveillance. The debate ended in 1982 with a resolution that the organization should become active in biological monitoring in parallel with developing TLV, but should not have a direct role in medical surveillance. ACGIH viewed biological monitoring as a measure of absorption, metabolism, or excretion of an industrial chemical and not as a measure of toxicity or health effect, thus attempting to distinguish it from medical surveillance (11).

### Creation of the Biological Exposure Indices Committee

In 1982, ACGIH Board of Directors appointed a new committee to develop reference values for biological monitoring based on the above philosophy. The charge to the committee was to review current scientific literature and recommend BEI that can be sufficiently documented. In addition, tentative BEI were to be suggested for chemicals for which useful but insufficient data or methods were available, as encouragement for generation of additional data.

The BEI Committee was organized in 1983 and included five members plus two consultants from private industry. The group developed a written description of the definition and interpretation of the reference values, together with six recommended values in 1984: the substances covered were carbon monoxide, ethyl benzene, styrene, toluene, trichloroethylene, and the xylene isomers. In accord with the procedures for the TLV, these recommendations were proposed to the ACGIH membership using a formal mechanism for eliciting comment (see procedure section) and adopted as the first Biological Exposure Indices in 1986. In subsequent years, BEI have been developed for 29 additional chemicals or groups of chemicals, and 7 existing BEI have been revised in response to appearance of new data in the scientific literature.

## Present Status: Procedure for Establishing Biological Exposure Indices

Establishing a BEI has evolved since the early days of the BEI Committee into a staged process consisting of *a*) feasibility analysis, *b*) development of a proposed BEI, *c*) formal publication of that proposal with an invitation for comment from all parties, *d*) review and possible revision of the proposal, and *e*) final adoption by the voting members of ACGIH. At each stage, the actions of the BEI Committee are subject to review by members of the ACGIH Board of Directors, who are elected in turn by the membership.

One of the critical decisions in the process is the initial one regarding the feasibility of establishing a new BEI. In the course of making this decision, the committee considers several criteria discussed in a written feasibility assessment prepared by one or two committee members. The criteria are listed below.

### Extent of Systemic Absorption and Disposition

Substances must be absorbed into the circulation to the extent that target tissues remote from the site of entry are affected and so that accessible biological fluids or tissues contain the chemical or its metabolite in detectable concentration. An industrial chemical with potent toxic properties that exerts its effect only topically or only at the site of absorption is not a candidate for setting a BEI, since biological monitoring is unlikely to generate information useful for preventing or minimizing exposure.

### Size of the Exposed Worker Population

Although there is no specific quantitative requirement for this aspect, data on the size of the population are needed. In general, exposures to workers should occur in more than a single industrial facility and preferably in the workplaces of more than one company. Equally important is the recent trend in these data, as a substance whose use in industry is decreasing may be of much less interest than one whose production and use are growing. The influence of this factor may be diminished for a substance with very potent toxicity for which other feasibility criteria are particularly compelling, such as the glycol ethers, which may penetrate the skin in significant amounts.

### Existence of a Threshold Limit Value for the Substance

The great majority of BEI are directly related to the corresponding TLV. They address the same health outcome and represent the expected internal dose corresponding to inhalation at the TLV. Exceptions to this criterion have been made in the past and establish a precedent for similar future exceptions where the other feasibility criteria argue strongly for establishing a BEI. The present exceptions are BEI for classes of compounds inducing methemoglobinemia and for those inhibiting acetyl cholinesterase.

### Humans Toxicokinetic Data Are Available

There should be sufficient data of high quality that describe the absorption, systemic distribution, metabolism, storage, and excretion of the compound or its metabolites. These are necessary to support the selection of the appropriate analyte, the tissue or fluid to be sampled, and the timing of the sample. The committee requires that the toxicokinetic studies be published in the peer-reviewed scientific literature so their quality can be assessed by all interested parties. In some instances, validated toxicokinetic models have been used where experimental human data were not sufficient. Further, toxicodynamic data may also be appropriate in instances where the anticipated BEI would be directly related to health effect rather than to an airborne concentration. This particular means of developing a BEI has been used only rarely to date.

### Analytical Chemical Methods Are Available

Data in the peer-reviewed literature must demonstrate that a method exists for assay

of the determinant with acceptable accuracy, precision, and sensitivity. These performance characteristics must permit analysis of the determinant in the recommended tissue or fluid sampled at levels both below and above the anticipated level of the BEI. Inadequate analytical methodology will preclude the development of a reference value.

An affirmative feasibility decision launches the development of a proposed BEI by one or two members of the committee. The written proposal will include the identity of the industrial chemical or category of substances addressed together with its CAS number and chemical formula. The recommended BEI includes the identity of all determinants—parent compound, metabolite(s), biochemical change—together with the medium to be sampled, the time of collection relative to the exposure period, and the numerical value of the index expressed as a concentration or percentage of normal. In many instances there will also be a notation that marks one or more special considerations for the BEI, such as the need to account for background levels in workers due to exposure outside the workplace. An example the contents of the BEI is shown in Table 1.

A proposed BEI is supported by a document that reviews the scientific data used in developing the reference value and that contains a synoptic rationale for the recommendation. The documentation must conform to a standard format incorporating relevant physical and chemical properties of the chemical; toxicokinetic data; discussion of possible nonoccupational exposure; the value and rationale for the corresponding TLV; a discussion of sampling and analytical methods for the determinant(s); anticipated biological levels without occupational exposure; the timing of appearance of the determinant; factors affecting interpretation of the measurement; the justification for the recommended BEI together with a critical assessment of the current data available; and finally, a description of

reference values recommended or required by other organizations. All literature used in the preparation of the documentation is cited and a copy of each item must be provided for archiving.

The BEI Committee then conducts a thorough review of the proposed BEI and its documentation. A member not involved in the preparation of the proposal is assigned to lead this review, during which special attention is paid to the correspondence of the BEI to the TLV if that approach has been used, or to the relationship to health effects data if not. Conformance to the feasibility assessment is considered and the practical aspects of sampling, analysis, and interpretation are examined. The review process is one of scientific judgment based upon the weight of available evidence and does not include a quantitative risk assessment. The approach in most cases has been to select the level of each determinant that is most likely to result from inhalation exposure at the TLV. The decision takes account of typical workers' physical activities during exposure and pays particular attention to experimental or epidemiologic data on the toxicokinetics of the compound. The final recommendation is invariably a consensus of the voting members of the committee. Revisions to the documentation are often agreed upon at this stage in response to comments from the committee members.

BEI recommendations from the committee are then reviewed by the ACGIH Board of Directors and, if approved, placed on the agenda of the ACGIH Annual Membership meeting for vote of approval by the members. A favorable vote at this point results in publication of the proposed BEI in the "Notice of Intent to Establish or Change." This appears in the booklet (5) published annually by the ACGIH containing the adopted and proposed values for all TLV and BEI and is a formal invitation for comment and criticism from all interested parties. Annual circulation of the booklet is over 100,000 copies worldwide.

**Table 1.** Example of the contents of each Biological Exposure Index.

Carbon monoxide CAS: 630-08-0 CO			
Recommended BEI determinant	Sampling time	BEI	Notation <sup>a</sup>
Carboxyhemoglobin in blood	End of shift	3.5% of hemoglobin	B, Ns
Carbon monoxide in end-exhaled air	End of shift	20 ppm	B, Ns

Abbreviations: B, determinant is usually present at a significant level in subject not occupationally exposed; Ns, determinant is nonspecific, since it is present after exposure to other chemicals. <sup>a</sup>Background levels are included in the BEI value.

Documentation of the proposed BEI is available from the ACGIH by request.

The proposed BEI must remain on the "Notice of Intent to Establish or Change" list for at least 1 year, after which the committee reviews all comments received as well as any new scientific data to emerge. Revisions may be made to the BEI and its documentation, after which another consensus is reached regarding adoption. If a proposed BEI is revised at this point, the new proposal must spend another year on the Notice of Intent list. After the required notice period, a recommendation for adoption is again reviewed by the Board of Directors and the ACGIH membership. Final adoption results in publication of the BEI in the booklet as an established reference value and incorporation of the new documentation into the three-volume set published by the ACGIH (12), which contains all the documentation for the TLV and BEI.

A significant aspect of the TLV and BEI procedure is the periodic reexamination of the adopted reference values. Generally the original authors of the documentation are expected to monitor the scientific literature for new data that may bear on the BEI. A proposal for revision may be presented at any time and can be acted on within one year of presentation. In this way the collection of BEI can be kept consistent with current science and thus will be of maximum utility to occupational health practitioners. The annual publication of the TLV/BEI booklet reveals numerous revisions as a consequence of this continued surveillance. The frequent updating of the ACGIH reference values stands in marked contrast to the much slower, legislatively mandated, process of the U.S. Occupational Safety and Health Administration in revising its regulations governing the same substances.

### Examples of Current Biological Exposure Indices

To shed further light on the decision-making process used by the BEI committee, several examples of recently adopted or revised BEI are described by summarizing the justification and rationale for the recommended reference values.

**Lead.** The BEI has been set at a level to prevent or minimize effects that are believed to result in persistent functional impairment of the worker or his or her offspring. Certain effects may be seen at blood lead levels below the BEI of 30 µg/dl. These are not believed to represent significant impairment either because the

effect is reversible or transient and is not likely to result in permanent impairment or because the body's reserve capacity sustains normal function despite a slight deficit in enzyme activity. The recommended BEI is intended to prevent or minimize:

- Psychological and psychomotor effects that appear at blood lead levels above 30 µg/dl but that do not exceed the reference values of the test methods (13);
- Changes in nerve conduction velocity and latency intervals, which also appear at blood lead levels above 30 µg/dl but have uncertain association with worker impairment (14);
- Decrements in the hematological reserve capacity reported in one study at blood lead levels above 40 µg/dl (15);
- Renal impairment, as measured by creatinine clearance and proteinuria, where minor changes that did not constitute functional impairment were reported at blood lead levels below 30 µg/dl and increased rates of proteinuria were reported at blood lead levels of 40 µg/dl and above (16,17);
- The occurrence of spontaneous abortions and effects on male fertility where some but not all studies reported positive associations with blood lead when the level was above 30 µg/dl (18,19);
- Decreased length of gestation and birth weight in offspring of exposed women, where study results are mixed and methods used were not universally accepted in the scientific community. Expert reviews conclude that if there is an association with blood lead, it occurs at levels above 30 µg/dl (20).

Clinical effects on renal function, bone marrow, and central nervous system are associated with blood lead levels of 50 µg/dl and higher (12).

The present lead BEI was adopted in 1995 and represents a departure from standard practice in that the reference value is based directly on the epidemiologic relationship to health effects rather than on the corresponding air concentration. The prior lead BEI was developed in 1987 and was linked to the contemporary TLV; with the rapid growth of epidemiologic data on lead exposure and health in both the general and working populations, the BEI committee was persuaded that a different approach was defensible. This appears to be the first instance in which the revised BEI is not closely linked to the TLV and may serve as a precedent, although few other substances of health significance have been so thoroughly studied by epidemiologists.

**Toluene.** The present BEI for toluene (set in 1986) includes hippuric acid in urine, toluene in venous blood, and toluene in exhaled air. The hippuric acid reference value has the most solid basis in experimental and epidemiologic data and is set to correspond to the contemporary TLV (21). The test is not specific, as there are dietary sources of other chemical precursors to hippuric acid, and therefore simultaneous measurement of toluene in blood is recommended as a confirming test. Although toluene in blood or breath is a specific indicator, toxicokinetic data indicate that the timing of sample collection relative to the end of exposure is so critical that these tests are not suitable alone for quantitative exposure assessment (2,22).

Recently the TLV for toluene was halved based on newer data associating exposure with effects on the central nervous system. The BEI is now under active consideration in response to this change, but the hippuric acid index poses some practical difficulties. Exposures at the new TLV would be anticipated to produce hippuric acid levels in urine that are at or below the background levels in persons without occupational exposure, based on studies in populations in western Europe and the United States (23). However, data from populations in Asian nations reveal significantly lower background hippuric acid levels, probably reflecting different dietary patterns (24,25). The use of the hippuric acid index in western populations may require very careful measurements of background and may not be feasible in some working populations. In other parts of the world this will not be an issue and the BEI can be revised in direct relationship to the TLV. Other specific markers of toluene exposure are being sought to address this problem.

### 2-Methoxyethanol and Its Acetate.

This is a recently proposed BEI presently on the Notice of Intent list. During the feasibility analysis for this set of compounds, it was apparent that toxicokinetic and toxicodynamic data are inadequate to serve as a basis for a quantitative index of exposure. The decision to proceed was based on the importance of these chemicals in industry and their adverse effects on reproduction (26) together with the availability of a suitable analytical method for the metabolite (27). The committee is therefore recommending monitoring 2-methoxyacetic acid in urine, collected after the last shift of the workweek, as an indicator of weekly exposure to either parent compound. No quantitative index

is established because of insufficient toxicokinetic data. However, the compounds are readily absorbed through the skin and dermal contact may be the primary route of occupational exposure (28). Because of the concern over potential reproductive effects from dermal exposure, skin contact should be minimized or prevented and metabolite monitoring offers a valuable measure of the effectiveness of control methods. Since the metabolite is not normally found in the urine of workers not exposed to the parent compounds, its presence is evidence of exposure by dermal and inhalation routes (29).

In developing this rationale, the committee has also proposed a special notation, Nq (nonquantitative), to highlight the circumstances under which a BEI is proposed with no value for the determinant level. Tentative criteria for assigning the Nq notation are *a*) health risk information and an analytical method are adequate; *b*) the number of workers potentially exposed is high and the quantity of chemical used is high; *c*) dermal absorption is a likely major route of uptake; *d*) background levels are low.

This pair of glycol ethers meets all of the criteria except the second; there is some doubt that the number of exposed workers continues to be high given the rapid changes in solvent use in the aircraft and other industries. Presently, however, sufficient justification remains for the proposed BEI with the nonquantitative notation.

The present list of adopted BEI is summarized in Table 2. For full details on each determinant, including the recommended sampling times and guidance on interpretation of results, the documentation (12) should be consulted.

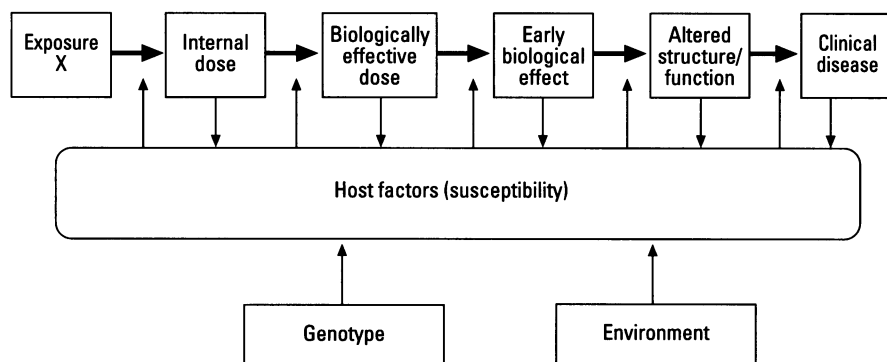
## The Role of Biological Exposure Indices in Occupational Health

### Bioindicators of Exposure, Effect, and Susceptibility

In establishing its reference values for biological monitoring, it is clear that the ACGIH has chosen to limit application of reference values to the early stages in the induction of occupational disease. Figure 1 is a schematic diagram of the interaction of environmental chemical exposure with host factors in determining individual susceptibility to disease. The progression from environmental exposure to clinical disease includes toxicokinetic processes that influence the internal dose—the concentration of the

**Table 2.** Compilation of current Biological Exposure Indices, with dates of adoption and revision.

Chemical agent	Biological Exposure Index	Reference value	First adopted	Last revised
Acetone	Acetone in urine	100 mg/liter	1994	
Aniline	<i>p</i> -Aminophenol in urine Methemoglobin in blood	50 mg/g creatinine 1.5%	1991	
Arsenic and soluble compounds including arsine	Inorganic arsenic metabolites in urine	50 µg/g creatinine	1993	
Benzene	Phenol in urine Benzene in exhaled air	50 mg/g creatinine 0.12 ppm	1987	Expected 1997
Cadmium and inorganic compounds	Cadmium in urine Cadmium in blood	5 µg/g creatinine 5 µg/liter	1988	1993
Carbon disulfide	2-Thiothiazolidine-4-carboxylic acid in urine	5 mg/g creatinine	1988	
Carbon monoxide	Carboxyhemoglobin in blood Carbon monoxide in exhaled air	3.5% 20 ppm	1986	1993
Chlorobenzene	4-Chlorocatechol in urine <i>p</i> -Chlorophenol in urine	150 mg/g creatinine 25 mg/g creatinine	1992	
Chromium (VI)	Chromium in urine	30 µg/g creatinine	1990	
Cobalt	Cobalt in urine Cobalt in blood	15 µg/liter 1 µg/liter	1995	
<i>N,N</i> -Dimethylacetamide	<i>N</i> -Methylacetamide in urine	30 mg/g creatinine	1995	
<i>N,N</i> -Dimethylformamide	<i>N</i> -Methylformamide in urine	40 mg/g creatinine	1988	1996
2-Ethoxyethanol and 2-ethoxyethyl acetate	2-Ethoxyacetic acid in urine	100 mg/g creatinine	1994	
Ethyl benzene	Mandelic acid in urine Ethyl benzene in exhaled air	1.5 g/g creatinine	1986	
Fluorides	Fluorides in urine	10 mg/g creatinine	1990	
Furfural	Furoic acid in urine	200 mg/g creatinine	1991	
<i>n</i> -Hexane	2,5-Hexanedione in urine <i>n</i> -Hexane in exhaled air	5 mg/g creatinine	1987	
Lead	Lead in blood	30 µg/dl	1987	1995
Mercury	Inorganic mercury in urine Inorganic mercury in blood	35 µg/g creatinine 15 µg/liter	1993	
Methanol	Methanol in urine	15 mg/liter	1991	1995
Methemoglobin inducers	Methemoglobin in blood	1.5%	1990	
Methyl chloroform	Methyl chloroform in exhaled air Trichloroacetic acid in urine Trichloroethanol in urine Trichloroethanol in blood	40 ppm 10 mg/liter 30 mg/liter 1 mg/liter	1989	
Methyl ethyl ketone	Methyl ethyl ketone in urine	2 mg/liter	1988	
Methyl isobutyl ketone	Methyl isobutyl ketone in urine	2 mg/liter	1993	
Nitrobenzene	<i>p</i> -Nitrophenol in urine Methemoglobin in blood	5 mg/g creatinine 1.5%	1991	
Organophosphorus cholinesterase inhibitors	Cholinesterase activity in red cells	70% of individual baseline	1989	
Parathion	<i>p</i> -Nitrophenol in urine Cholinesterase activity in red cells	0.5 mg/g creatinine 70% of baseline	1989	
Pentachlorophenol	Pentachlorophenol in urine Pentachlorophenol in plasma	2 mg/g creatinine 5 mg/liter	1988	
Perchloroethylene	Perchloroethylene in exhaled air Perchloroethylene in blood Trichloroacetic acid in urine	10 ppm 1 mg/liter 7 mg/liter	1989	1996
Phenol	Phenol in urine	250 mg/g creatinine	1987	
Styrene	Mandelic acid in urine Phenylglyoxylic acid in urine Styrene in venous blood	300 mg/g creatinine 100 mg/g creatinine 0.02 mg/liter	1986	
Toluene	Hippuric acid in urine Toluene in venous blood Toluene in exhaled air	2.5 g/g creatinine 1 mg/liter	1986	
Trichloroethylene	Trichloroacetic acid in urine Trichloroacetic acid and trichloroethanol in urine Free trichloroethanol in blood Trichloroethylene in blood Trichloroethylene in exhaled air	100 mg/g creatinine 300 mg/g creatinine 4 mg/liter	1986	
Vanadium pentoxide	Vanadium in urine	50 µg/g creatinine	1995	
Xylenes	Methylhippuric acids in urine	1.5 g/g creatinine	1986	



**Figure 1.** Interaction of factors leading from chemical exposure to disease, including the effects of susceptibility. Adapted from Van Damme et al. (30). →, toxicokinetic or toxicodynamic relationships; ↑ ↓, modifying effects.

substance or its metabolite in biological media—and the biologically effective dose—the concentration at the target tissue or cells (31). Subsequent biological processes lead to early biological effects associated with the mechanism of disease followed by changes in structure or function that can be detected clinically and are predictors of disease, followed in turn by clinical disease (11). Individual (host) factors modify the progression from each step in the process to its successor and the collective influence of the host factors is termed susceptibility. Variation in the host factors is influenced by genetic determinants and other environmental exposures.

Biological indicators, or biomarkers (31), are often classified as addressing exposure, effect, or susceptibility, based on this general schematic. The application of the BEI reference values has been limited to the early stages in the process: internal dose, biologically effective dose, and in a few cases, early biological effect. The indicators used in the BEI are therefore best considered biological indicators of exposure, with the acknowledgment that their level in an individual reflects the influence of susceptibility. In addition, since a few of the BEI are consistent with monitoring early biological effects, their application may be thought of as biological monitoring of response. Clear distinctions between markers of exposure and those of effect remain elusive.

### Use in Preventive Measures

Regardless of the term applied to biological monitoring using the BEI as reference values, its most important characteristic is that this type of monitoring is part of the strategy to prevent exposures that might otherwise lead to occupational disease. Conversely, the BEI are not appropriate for use in identifying susceptible individuals or in demonstrating the presence of preclinical

or clinical disease. Evaluating the latter stages of the exposure–disease process is certainly a legitimate application of other forms of biological monitoring such as evaluation of mutations, clastogenic effects, or the presence of disease markers such as  $\beta_2$ -microglobulin; such later stage monitoring does not play a role in primary prevention of disease (11,32).

Since the principal function of industrial hygiene is the prevention or minimization of occupational disease through control of chemical exposures, the limitation used by the ACGIH for its BEI is appropriate. Further, biological monitoring of exposure using these reference values is complementary to ambient environmental monitoring performed by industrial hygienists and other occupational health specialists. The results of biological monitoring will provide additional information regarding the conditions of occupational exposure, which cannot be obtained by sampling the air of the workplace: the consequences of skin absorption, the effects of physical workload on chemical uptake via inhalation, and the effectiveness of personal protective equipment in reducing worker exposure are three important examples. It must also be emphasized that biological monitoring cannot substitute for air monitoring in the context of exposure prevention: a high biological result alone will indicate possible excessive exposure but will provide no information on the likely source or mechanism of over-exposure. Choosing an appropriate course of action for control of the hazard requires information beyond that obtained from biological monitoring alone (7).

### Key Characteristics Expected of Biomarkers of Exposure

Based on the premise that exposure prevention will continue to be the major application of biological monitoring and of the

BEI in industrial hygiene, the following attributes can be identified as critically important in the development of new methods and reference values. These characteristics should be expected of any biomarker proposed for application to preventing occupational exposure and disease.

**Correlation with Exposure.** The level of the biological indicator must be related clearly to the intensity and the duration of exposure in humans (33). This relationship must be demonstrable at levels of exposure found or expected in industrial settings. The analytical limits of quantitation of the biological determinants must span the range of occupational exposures.

**Correlation with Target Tissue Dose.** Because the actual target tissue is seldom accessible for sampling, surrogate fluids or tissue must be used for biological monitoring. The most common samples are peripheral blood, voided urine, and exhaled air. Depending on the target tissues, these samples will reflect with variable accuracy the biologically effective dose (33–36). Reliable information on the relationship between biological indicator level in peripheral blood or urine and in the target tissue is highly desirable.

**Appearance Is Reversible.** The reversibility of the biological indicator may be most important in distinguishing industrial hygiene applications from other uses of biological monitoring (34,37,38). Since the goal is prevention, the industrial hygienist will be most interested in a biological indicator that reveals the effectiveness of control measures adopted after a judgment of hazardous exposure has been reached. If the indicator is irreversible, its appearance will alert the hygienist to a potentially hazardous situation but will not provide evidence that mitigating measures are working.

**Influence of Confounding and Modifying Factors Is Well Characterized.** To interpret the results of biological monitoring correctly, the influence of modifying and confounding factors must be understood. These factors include the effect of nonoccupational exposure to the agent of interest, prior or simultaneous exposure to other agents, host factors modifying the response, and the general influence of variation in environmental and individual response (36).

**Suitable for Application in Working Populations.** Some types of biological sampling are too invasive or risky for use in the workplace and others may not be acceptable to workers for a variety of reasons. Adipose tissue, liver, or bone marrow

sampling are examples of the former type. In any successful application of biological monitoring, the workers' cooperation must be secured. For example, when samples must be collected several hours after the end of a work shift to interpret the results properly (39), it is clear that the individuals must take major responsibility for valid sampling. Any procedure perceived by the workers to be unpleasant or unnecessary likely will not be followed (32,40).

### Current Issues in Setting and Revising Biological Exposure Indices

A variety of stimuli and challenges will arise in the course of revising the existing BEI and developing new ones in the next decade. These include scientific advances in biological marker analysis and their relationships to disease and technical issues related to the interpretation of measurements in an individual worker. In addition, there are some important nonscientific impediments to the implementation of biological monitoring that may slow the process of developing reference values.

#### Development of New Methods for Markers of Early Biological Effect and Susceptibility

**DNA and Protein Adducts.** The ability to determine the extent of reaction between environmental chemical agents and biological macromolecules such as DNA and proteins is developing at a dramatic rate. The appearance of DNA adducts in peripheral blood lymphocytes and of hemoglobin adducts in blood have been proposed as markers of biologically effective dose or early biological effect. A less-invasive method based on collection of bladder epithelial cells in voided urine has also been described (41). In some cases these adducts can be shown to be specific to an environmental agent or group of agents, but in other cases the adducts are not specific (37). In addition, there remain questions about the relationship of adducts appearing in peripheral blood to genetic damage presumed to occur within the target cells (40,42).

**Chromosomal Aberrations, Sister Chromatid Exchange, and Micronuclei.** Structural changes in chromosomes and other microscopic evidence of damage to chromosomes, including the appearance of micronuclei are also possible candidates for occupational biological monitoring methods. This form of monitoring is most often classified as indicating altered structure or function and occasionally as an

indicator of early biological effect. In either event, the reversibility of the marker is an important characteristic that will influence its role in the development of BEI values. Insufficient data presently exist concerning the sensitivity and specificity of these assays at levels of exposure encountered in the workplace (43).

**Genetic Markers of Exposure and Susceptibility.** Another developing area of macromolecular biology is the analysis of genetic material as an indicator of the activity or inducibility of enzymes in an individual (37). The variation in activity of enzymes mediating phase I and phase II metabolism of absorbed chemicals will affect individual response to exposure in a manner that can be predicted. Expression of enzyme activity is under genetic control, as is the response of enzyme activity to environmental exposures to the substrate itself or to other chemicals (42). Characterization of an individual's genotype can provide markers of exposure to inducing chemicals or markers of susceptibility to later exposure.

#### Nonscientific Impediments to Implementation

The practice of biological monitoring in U.S. industry has been limited by an array of social, political, and legal factors (44), many of which remain to be addressed. Labor mistrust of management motives in proposing biological monitoring is widespread and is often predicated on the objections to invasion of privacy or suspicion that the employer is actually seeking evidence of drug abuse to use against employees. Company managers have, in turn, objected to proposals for biological monitoring on the grounds that there is rarely a regulatory mandate and that adverse findings might leave the employer subject to legal action.

It has also been argued that the personalized results of biological monitoring could provide an employer with the data to support discriminatory action against, for example, employees demonstrating genetically determined susceptibility to agents in the workplace (45). Further, should a worker be identified to be at elevated risk due to personal biological factors such as hereditary variation in metabolizing capability or environmentally induced change in toxicokinetic processes, there is not commonly a policy in place for fair treatment: financial coverage for medical removal or job transfer is seldom planned for by the employer.

The principle of confidentiality of medical records has at times interfered with the

use of biological monitoring data by industrial hygienists. In keeping with the goal of preventing or minimizing exposure, the industrial hygienist must have access to such data to conduct a complete exposure assessment; at the same time, workers' rights to confidentiality should be maintained and the management scheme for accomplishing these often contradictory goals must be developed carefully in advance.

#### Scientific Impediments: Variation and Background

Several technical and scientific issues pose obstacles to widespread use of biological monitoring and BEI in industrial settings where they could provide valuable information (34). These include matters of ambiguity in interpretation of the BEI and the consequences of the general decline in exposure levels in most industries with time.

Variability over time in biological levels of an indicator within an individual and between workers at the same time must arise when the environmental concentrations fluctuate. However, variation in toxicokinetics both within and between workers also contributes and this component can dominate the observed variability (46,47). This poses substantial difficulty in interpreting a single biological monitoring result by comparison to the BEI: if the result exceeds the BEI, is this evidence for a hazardous exposure? The BEI Committee has taken a general approach to this issue by advising that due to biological variability it is possible for an individual's measurement to exceed the BEI without incurring an increased health risk. If, however, measurements in specimens obtained from a worker on different occasions persistently exceed the BEI or if the majority of workers at the same workplace exceed the BEI, the cause of the excessive values must be investigated and control measures must be implemented. This suggests that in some instances the group mean rather than the individual values should be compared to the BEI and that serial measurements may be necessary. Present data concerning individual variability are not sufficient to place more precise limits on the acceptable range of values about the BEI. However, some techniques have been described recently for predicting the expected distribution of biological levels among normal workers with realistic variation in toxicokinetic parameters (48,49). As these techniques become refined, it should be possible to specify the BEI as a reference distribution (37,50) rather than a single value, permitting



estimation of the probability of a worker showing an observed biological level when exposed at or below the TLV. Using this approach, the development of confidence or tolerance intervals for workers or groups of workers should enhance the utility of biological monitoring of exposure and of the BEI recommendations.

In many western nations, particularly in the larger industrial facilities, there has been a steady decline in exposure levels over time owing to developments in both industrial technology and hygienic practices. A significant consequence is that biological levels in workers in these industries have also declined and in some instances are now comparable to background levels found in persons without occupational exposure (32). Many industries using lead and toluene are examples. Further, the lowering of acceptable air concentrations, driven in part by revisions in the TLV, also contribute to this trend. If reference values for biological monitoring are revised downward in concert with TLV, they will overlap background levels with increasing frequency. Fluctuation in background may then cause individual measurements in workers to appear to exceed the BEI, leading to a conclusion that a hazardous situation exists. If the BEI is based on a direct relation to health effect (as is now the case for only a few substances), then this conclusion would be correct, even though the major source of exposure to the hazard is now outside the workplace. However, if the BEI is based on a corresponding dose from inhalation at the TLV, the assessment is ambiguous. If exposure by other routes is possible, simultaneous measurement of air concentration in the workplace will not resolve the problem completely. Clarification of this ambiguity in interpretation remains one of the responsibilities of the committees charged with setting the TLV and BEI. For example, rather than including background, the BEI might be described as representing the increment above background in biological level of a marker that would be expected to result from inhalation exposure at the TLV. This subtle but important change has been suggested, but its implications have not been thoroughly examined.

## Prospects for the Next Decade

### Legal and Regulatory Environment

The regulatory status of biological monitoring in the United States is rather limited; only for lead and cadmium do federal

occupational safety and health regulations require employers to provide biological monitoring of workers. In addition, it is not clear that the government has the authority to require workers to submit to biological monitoring (45). Because of the slow process involved in setting or revising these regulations and the impediments mentioned above, this situation does not appear likely to change in the near future. Many employers, most of them large corporations, have voluntarily implemented biological monitoring programs for substances such as fluorides, mercury, and cobalt, but a systematic evaluation of the prevalence of biological monitoring programs in the United States has not been reported.

One important feature of this unsettled regulatory picture is the balance of cost versus benefit for biological monitoring. This type of sampling is more labor intensive than air sampling and often requires the participation of qualified health care specialists. In addition, the chemical analysis of biological matrices is technically more difficult than that of air samples. As a result, the cost of biological monitoring per sample taken is substantially higher than that for air sampling. It has been suggested that the benefits of biological monitoring seldom outweigh the costs, particularly when the possibility of legal action arises over high values or when medical removal and employee compensation must be provided. Others have argued that if a complete accounting of all costs and benefits associated with preventing work-related disease and compensation is done, biological monitoring will prove to be economical (45).

### Scientific Developments

**Genetic Analysis for Evidence of Exposure or Susceptibility.** Methods for determining the genotype of individual workers are developing very rapidly. One of the most interesting approaches is the measurement of enzyme-specific mRNA as an indicator of exposure to a substance capable of inducing the enzyme. Methods employing reverse transcription combined with polymerase chain reaction amplification may have sufficient sensitivity and specificity to detect exposure to carcinogenic agents or cigarette smoke at low levels (51). Studies of the expression of mRNA in chemically exposed populations are in progress and may lead to a powerful method for individual biological monitoring of exposure.

One of the major factors determining individual differences in susceptibility to chemical exposure is variation in metabolic

handling of solvents and other agents (33). The existence of genetically determined bimodal or multimodal distributions of metabolizing capability in humans has been known for some time (52). For example, the ability to oxidize debrisoquine, mediated by one of the cytochrome P450 isoenzymes, shows a bimodal distribution in the Caucasian population and this genetic dimorphism is associated with similar differences in rates of metabolism of certain industrial chemicals (53). There is a similar genetic polymorphism in the rate of conjugation of metabolites mediated by *N*-acetyltransferase (42). The ability to classify workers based on their genotypes into susceptible subgroups is nearly at hand and could have important applications in preventing work-related disease.

**Advance of Analytical Sensitivity and Specificity.** Steady improvement in the limit of detection, sensitivity, and specificity of analytical chemical methods supports the view that biological monitoring methods will continue to advance. Determination of macromolecular reaction products that are specific to the industrial chemical agent will be of special interest. Advances in analytical performance must be accompanied by quality control procedures (37) and by continuing careful assessment of all sources of variation in observed levels of the biological determinant.

**Better Sampling Techniques.** The lack of strong correlation between some biological indicators of exposure and the biologically effective dose at the target tissue remains a significant concern. One potentially useful approach to this problem is the use of methods to determine the level of a chemical agent or its metabolite *in situ* without withdrawing a tissue sample (33). Two techniques have been described for accomplishing this: neutron activation analysis for determination of cadmium in kidney and liver tissue, of mercury in brain, kidney, and liver tissue, and of silicon in the lungs as a marker of crystalline silica exposure; and X-ray fluorescence analysis of lead in teeth and bone, of cadmium in kidney and liver, and of mercury in the kidney (54). Both methods are technically complex, requiring the use of costly instruments, and they also involve absorption of doses of ionizing radiation that are significant relative to background exposures in the general population. The ability to locate the contaminant within a selected target organ is the principal advantage of these techniques. Their application may be limited to situations in which the long-term



accumulation of toxicant or metabolite must be evaluated to assess risk.

Additional research is also needed to develop and improve less invasive methods of sampling fluids or tissues for biological monitoring. Sampling of hair, fingernails, and sweat have been explored and largely dismissed owing to problems of contamination from sources external to the circulation. Exhaled breath and saliva remain promising fluids whose collection poses considerably fewer problems than that of blood or urine. However, breath sampling is still hampered by analytical limitations imposed by the high concentrations of water vapor and carbon dioxide (55) and by the relatively low concentrations of volatile agents after typical occupational exposures. Improvements in analytical methods should support wider application of breath sampling. Saliva sampling has been proposed recently as a practical method for monitoring occupational exposure, based on data from experimental animals showing a strong correlation between plasma levels of selected pesticides and their concentration in saliva (56) and on a reported method for determining cadmium in saliva (57).

**Better Data on Toxicokinetics and Overall Pathophysiology.** While each of the above developments is cause for excitement and optimism, none will find wide application in occupational biological monitoring until considerable data are collected on the toxicokinetics and overall pathophysiology of the markers and their associated exposure or effects. There remains a serious shortage of data from both experimentally controlled exposures and epidemiologic investigations that are essential to support the adoption of a biological monitoring method and, in particular, of a reference value. There are some obstacles to expansion of these research activities, including ethical concerns over controlled experimental exposures of human volunteers to potentially toxic agents. Greatly improved analytical sensitivity and specificity for chemicals or metabolites in tissues may permit use of controlled doses in humans that are at or below those occurring in current occupational settings (58). That trend could relieve some of the concern over the risk and benefit balance for clinical experimentation in this area.

For biological markers of early response and susceptibility, an additional ethical concern has been articulated (59). For example, if in an epidemiological study of a biomarker of effect aimed at determining

its prevalence and reliability as a function of exposure, early on its prevalence is elevated in certain workers, it may be very difficult to complete the study: the employer may wish to modify the working conditions to lower exposures on the basis of early appearance of a biomarker that could be associated with health risk. While this decision would be fully defensible in view of the desire to prevent adverse health outcomes, it could be devastating to the research design. Epidemiologists pursuing data that are essential to the validation of biological markers in exposed working populations must be prepared to deal with this problem.

Access to worker populations for epidemiologic research is also constrained to some extent by the need to plan for possible compensation costs should workers in the study reveal evidence of early biological effects. Many employers are unwilling to permit such investigations in their facilities on the grounds that the risk of subsequent litigation and compensation cannot be undertaken. It may be necessary to include thorough discussion of how various outcomes will be managed, with respect to communicating with workers and to providing for adverse results whether perceived or real, in the planning of epidemiologic investigations (45,60).

### International Cooperation

Other nations and organizations have developed reference values for biological monitoring. The most extensive are the Biological Tolerance Values (BAT) of the German Research Society (38,40); reference values and methods have also been developed in the United Kingdom, in Japan, and by nations of the European Community (6,7,61). In many cases the reference values are similar, but there are significant differences in both the approach to setting biological reference values and in their interpretation (38). For example, the BAT are established as maximum tolerable levels (40); in Japan, the values are specified according to a reference distribution with three levels (62); whereas in the United States, the ACGIH values are generally linked to air concentrations and apply to nearly all workers. The different approaches are the principal explanation for differences in the specific reference values; geographic variation in background levels may also influence the reference levels (50). There is considerable interest among many organizations in developing more uniform international criteria for biological reference values (63). Such international harmonization of

criteria could be beneficial to employers, workers, and scientists.

### Summary

The BEI established by ACGIH can play a significant role in the evaluation and control of exposure to hazardous chemicals in the workplace. These reference values have been developed by a small committee of scientists and occupational health professionals as suggested guidelines for judgment of the acceptability of biological monitoring results in exposed worker populations. At present the BEI specify the level of industrial chemical, metabolite(s) or biochemical change related to exposure and most indices are linked to the corresponding TLV. New BEI and revision of existing reference values will take into account scientific advances in toxicokinetic and toxicodynamic understanding, as well as new developments derived from research in macromolecular biology, including genetic markers of susceptibility and early biological effect. However, the underlying requirements for application of biological monitoring of exposure will continue to dominate decisions for new BEI in the next decade; the biological indicators must be correlated with exposure and with levels at the target tissue, they must be reversible, they must be well characterized with respect to the influence of modifying and confounding variables, and they must be suitable for practical application in working populations. Several impediments to wider application of biological monitoring of exposure, susceptibility, and early effect may be overcome in the near future, leading to more effective prevention of occupational illness and disability.

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